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# WHY USE SCIENTIFIC LITERATURE IN CLINICAL DECISION MAKING

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## INTRODUCTION

The human mind is pretty good at properly linking cause-and-effect when the initiating cause and outcome are easily detected with human senses, straight-forward with no interactions, and closely spaced in time and location. However, if either a causative factor or its outcome is undetectable by human senses aided by technology; or if multiple causes either must or can interact to bring about the outcome, the human mind makes many erroneous conclusions. Many of these problems exist in veterinary medicine, in that nearly all causes of disease and repair are completely outside the ability of human senses to detect even when aided by advanced technology, the time-frame between a causative factor and a clinically important outcome can be prolonged (with many other visible factors occurring in the interim time), and very slight or undetectable changes in homeostatic mechanisms can result in profound changes in perceivable disease or repair outcomes (with more-easily detectable – but wholly non-influential changes occurring prior to disease or repair outcomes). Fortunately, veterinary medicine can be a data-rich area of scientific investigation. Even though many of the factors affecting animal disease and repair are difficult or impossible to detect, the outcomes (recovery, length of life, improved growth, etc.) are readily measurable and occur within reasonable time-frames. In a science like veterinary medicine, our investigations of nature can be data-driven because of the relative ease of collecting clinically important outcome data.

### Limitations of Clinical Experience

- While clinical experience provides important observations about disease onset risk factors, therapeutic intervention efficacy and patient prognosis, clinical observations lack controls for bias and confounding and as such must be tempered with data from controlled experiments.
- Biologic systems are inherently more complex than other natural systems. Only biologic systems have complex homeostatic controls as well as the capability to remove insults, self-repair, and substitute for deficient factors.
- In addition, the hierarchy of: tissues, animals, intra-animal ecosystem, animal herds, animal populations, and ecosystems adds complexity that is absent in other natural systems.
- Simple experiments with small sample size and only rudimentary controls for bias and confounding and no statistical tests to differentiate between random chance and treatment effects were used to gain great insight into the sciences of chemistry, astronomy, and physics throughout history. In contrast, until the development of specific strategies in the first half of the twentieth century to design experiments with the purpose of controlling bias and to rigorously analyze hypotheses with statistical tests, advancements in disease prevention and treatment were slow or non-existent.[1,2,3]
- While every research study has important limitations in either internal validity, external validity or both, well-designed studies have incorporated at least some level of control for bias and confounding and use statistical tests to distinguish treatment effects from random variation.

- The reasons that for hundreds of years medical sciences lagged behind mechanical and other sciences are the same reasons that veterinarians today must embrace the scientific method and the results of rigorous, well-designed studies that control for variation, minimize bias, and effectively explore interactions.

## Attributes of veterinary medicine: random variation

- Veterinarians continually witness the phenomena of random variation of animals and biologic systems in that every practitioner is aware of the range of behaviors, laboratory and imaging indices, and growth and reproductive performance inherent in the species with which one works.
- We recognize that animals treated identically exhibit a range of average daily weight gain, pain tolerance, response to anesthesia, immunologic response to vaccination, and countless other examples. Differentiating the expected variation in response between animals treated identically from the effects of an intervention requires careful collection of data and probability calculations (e.g. statistical tests) unless the magnitude of treatment effect is so large as to be obvious.
- Many of the diagnostic, therapeutic, and prognostic questions that we investigate are concerning subtle differences that are impossible to identify without careful data collection and statistical tests.

## Attributes of veterinary medicine: biased and confounded observations

- Clinical experience is particularly prone to bias because the same person provides and then evaluates interventions.
- Biases that occur commonly, and often inadvertently, when relying on clinical experience are typically grouped into categories of selection bias, information bias, and confounding.
- Observations in clinical settings are plagued by selection bias because although this bias is a crucial flaw if one wants to compare interventions, it is perfectly appropriate and beneficial when applied to clinical case management. Essentially, selection bias occurs when animals with certain signalment, history, or physical examination findings are treated differently than animals without those case characteristics. While clinically reasonable, this practice prevents any attempt to accurately compare alternative risks or treatments.
- Information bias is very common in clinical case management because we intentionally gather different types and amounts of information about different animals. For example, it is reasonable to observe some animals more closely, under different circumstances, or for longer periods of time than other animals. However, this bias can lead to incorrect associations with either disease-causation or treatment factors.
- Confounding can occur when two potential causative factors are correlated but not evenly distributed and it is not clear which factor is causing the outcome of interest.
- Because many risk factors for disease tend to occur clustered together, confounding is a common problem when using clinical experience to make causation or treatment efficacy associations.
- Without careful statistical control, it is impossible to determine which of two confounding factors is the most important factor associated with a disease outbreak or therapy success. Controlled, well-designed experiments use a number of tools including random allocation of animals, blinding (aka masking) of observers, and extensive data collection to combat bias and confounding.

## Attributes of veterinary medicine: complex interactions

- Another limitation of clinical experience is the difficulty for the human mind to detect and quantify multiple relationships between two or more factors that affect clinically important outcomes.
- Because of the multi-faceted nature of most diseases and the complexity of disease avoidance, health outcomes are rarely influenced by a single factor.
- Factors that may interact to affect disease onset or recovery include age, sex, breed, stress, nutritional status, and concurrent exposure to other infectious, toxic, or metabolic insults.
- Interactions usually involve many variables, making it essentially impossible to accurately determine the entire causal web involved with disease onset or recovery, and to extrapolate clinical experience in one setting to other situations.

## The role of scientific literature in critical thinking

- Critically thinking about a clinical problem involves repeating the steps of gathering information, evaluating that information, reflecting on the information and coming to tentative conclusions.
- Because no single study can fully address most clinical questions and because every study has limitations either in internal and/or external validity, using scientific studies to enhance clinical decision making requires combining different pieces of evidence of varying strengths.
- While gaining competence in each step of the critical thinking process requires education, skill, and experience, probably the most difficult to master is to reflect deeply about what is known and what is unknown and how to tie multiple pieces of information and evidence together.
- Good clinical decisions are based on good critical thinking skills. Because the quality of thinking is limited by the amount and accuracy of pertinent information available, gaining competence to access, evaluate, and integrate the scientific literature is critical for developing good critical thinking skills.
- However, good information literacy skills does not guarantee good critical thinking skills in that a person with poor critical thinking skills may accrue very limited benefit from gaining access to valid scientific studies.

## Determining applicability of research findings

- Reading literature with a focus on answering a specific clinical question(s) is critical to avoid over-interpreting preliminary data or extrapolating beyond the true findings of the authors.
- Individual manuscripts are driven by research hypotheses created by the author(s) and these hypotheses drive the experimental design, outcome variables and interpretation of the results.[4] One of the first questions that should be posed is whether or not the research is clinically relevant to the reader's situation?
- Outcomes depicting clinically meaningful animal response to a specific health management technique such as risk of disease onset, risk of death, or length or quality of life can directly influence clinical decisions (assuming well designed research with patient comparability).
- When provided measures of response that only have indirect clinical importance, the reader is left to extrapolate what that response means in terms of potential success for disease prevention or

resolution and caution should be used when applying a treatment where no data exists regarding direct clinical outcomes.[5]

- Biologic and epidemiologic differences between the study population and the population which prompted the clinical question should be considered as a part of patient comparability.[6] If the research population is similar to the population on which the veterinarian expects to apply the health management technique, then research results are directly applicable. However, if the work was done in a different target population, the reader is forced to extrapolate findings beyond the study population, leading to potential errors in interpretation.
- For some clinical questions, very few clinical research study reports exist and the practitioner must extrapolate from other species or *in vitro* work to estimate the potential effect of health management techniques to the population of interest.

## Interpretation of the Results of Statistical Tests

- The purpose of statistics is to enable the reader to interpret study findings beyond the raw data and extrapolate study observations to other populations.
- Internal study validity should be assessed prior to interpretation of any statistical results. Internally valid studies collect data in a repeatable manner while controlling for bias through a research design that removes or controls unnecessary factors that could inadvertently influence study outcomes. Statistical tests do not evaluate if data are biased; therefore, studies with low internal validity should not be used for clinical decision making regardless of the statistical results.
- Statistics influence the final conclusions drawn by the authors and readers, and if incorrect statistical methods are used the study results can be nonsense at best and misleading at worst.[7]
- Interpreting statistics should always be done with a clear understanding of the research hypothesis. Evaluating the hypothesis(es) prior to reviewing the statistics will modify the types of conclusions that can be drawn from the study. A study with a single confirmatory hypothesis can be used to change clinical decision making, while a study with several exploratory hypotheses is best interpreted as a project generating future hypotheses to be tested.

## Clinical interpretation of study results

- Common errors that may invalidate research findings can be identified by becoming familiar with the typical methods used to: control for bias, ensure appropriate replication of experimental units, and deal with the structure of research data or populations.
- Published literature meeting the relevant criteria for valid, unbiased research should be incorporated into the clinical decision making process. However, inferences based on research results should be tempered by the study outcome selected, the patient comparability, and the number of appropriate studies available to assist the decision making process.
- Finding multiple, well-designed studies that address a pressing clinical question is not always possible and often the findings from a single trial are all that are available to support a clinical decision.

- Results should also be interpreted within the limits of the study, being careful to avoid extrapolating beyond the study population and time frame. This is challenging and one of the reasons that building true scientific knowledge is a relatively slow process.
- It is important to recognize that readers have inherent pre-existing beliefs when reviewing literature. Pre-existing knowledge makes it easy to believe the results of some research and very difficult to believe other findings, even when all studies were well-designed and conducted in a valid manner. Incorporating prior beliefs into study interpretation is valid as long as both the past belief and new information are rigorously tested and unbiased.[8,9]
- Forming scientific opinions is an iterative process and knowledge builds over time, with the most certain knowledge being supported by the aggregate findings of multiple studies.
- The scientific method of understanding biology and veterinary medicine is not a purely data-driven, mathematical process; in fact, the powers and limitations of human thought and decision-making are an important component of data interpretation from well-controlled trials and in the assimilation of results from multiple studies.

## Evaluating the body of evidence

- Although all or most veterinary clinical decisions are based on evidence of some type, some evidence is very strong (rigorously tested in the target-species under natural conditions in experiments designed to prove a theory to be false) and some is very weak (not tested) and some is intermediate.[6,10,11]
- The body of evidence relevant to answering clinical questions is the sum of multiple studies investigating the same area of interest and each study can be ranked on a scale from weak evidence to very strong evidence.
    - The first consideration is the internal validity of the research - which is determined by the study method and appropriate use of controls for bias. Research reports with good internal validity provide assurance that the results represent an unbiased estimate of the true direction and magnitude of the treatment effect. The strength and quality of evidence in a published study can be assessed by determining if the assignment of patients to treatments was randomized and if the caregivers and clinicians were blind to those assignments. Studies in which treatment is allocated by any method other than randomization tend to show larger and frequently false-positive treatment effects than do randomized trials.[12,13,14] It is also important that all animals in a group or treatment were evaluated (even drop-outs) and that all groups were treated equally except for the experimental therapy. In addition, it is important that the trial last long enough to recognize both potential positive and negative outcomes.
    - The second consideration is the population used in the research and its appropriateness as a model for the population that generated the clinical question. Generally, the target species in similar housing and husbandry environments provides stronger evidence than the target species in significantly different housing and husbandry environments, related species, unrelated species, or in-vitro methods.
    - And thirdly, the clinical relevance of the outcomes of the research should be considered with patient-/herd-oriented outcomes providing more direct evidence than disease-oriented outcome measurements such as concentrations of blood constituents.

- If it seems that the study results are valid, the second question one needs to ask is, are the valid results of this individual study important?
    - The true magnitude of effect of a therapy can never be known, but a valid trial provides a point estimate around which the true effect is expected to lie. The 95% confidence interval of the point estimate of the treatment effect is commonly reported to communicate the precision of the estimate of the treatment effect, and indicates the range that includes the true treatment effect 95% of the time.
    - The larger the sample size the greater is one's confidence that the true treatment effect is near the point estimate (narrow 95% confidence interval).
- And finally, if a study appears to be valid and important, are the valid, important results of this study applicable to my client's patient or herd?[15]
    - If the study animals or treatment setting is sufficiently different from your patient/herd that initiated the question, or if the treatment is either not feasible or not consistent with the client's/manager's values and expectations, a valid and important therapy would not be applicable in your current situation.
    - For a reported trial to influence treatment strategies, one should ask whether the outcomes of most importance to you, the clinician, and the owner/manager reported.
    - Even when a report indicates one or more positive outcomes associated with a treatment, one should consider whether other negative outcomes are also associated with that treatment. This is particularly important if the negative outcomes are more important to the owner/manager than are the positive outcomes.

## Limitations in the use of scientific literature in clinical decision making

- By knowing the strength of evidence for potential interventions, veterinary practitioners will often be less certain of his/her diagnostic, therapeutic, and prognostic pronouncements compared to client expectations for greater certainty.
- Expectations of the client for certainty and clarity may be at odds with the skeptical, methodical, testing-rejecting-retesting pace of the scientific method.

## SUMMARY

Practicing high-quality medicine by incorporating scientific literature into veterinary practices leads one to establish a problem-solving process that recognizes the important limitations that bias and complex interactions places on our ability to gain knowledge about animal health through clinical observations, and the value that well-designed studies provide to reduce bias and explore some aspects of complex interactions. However, understanding how to use the scientific literature in clinical practice also requires that one recognizes the limitations that even well-designed studies have incomplete control of bias and have limited ability to explore complex interactions. And, finally, integrating scientific literature into high-quality veterinary practice causes one to realize that gaining accurate knowledge is a very slow, iterative process with no short-cuts for the complex problems commonly encountered by veterinary practitioners.

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